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Final Report
of the
Mid-Program Evaluation

Florida A & M University

June 28-29, 2004

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ARCH Mid-Program Evaluation
Florida A&M University
PI: Renee Reams, Ph.D.

Executive Summary

The review committee visited Florida A&M University (FAMU) on June 28,2004. The review was to evaluate the progress of collaborative research and interactions between the scientists at FAMU and their counterparts at Wayne State University. Specifically the review team was to evaluate the administration and planning of the ARCH program, the research projects, the pilot projects, the process for selection of new pilot projects, the facility cores, the institutional commitment, and to determine if FAMU had benefited from the ARCH program. The overall evaluation of the FAMU/Wayne State ARCH Program determined that there has been progress in the successful development of the research infrastructure at FAMU. The programmatic collaboration has resulted in the establishment of a Cell Culture Facility, a Flow Cytometry Facility and a Molecular Methods Facility. These facilities are fully operational and under the direction of FAMU investigators. However, there are areas that need significant strengthening. A major concern regarding the FAMU-WSU ARCH program is in the area of productivity and mentoring. No peer-reviewed publications have resulted from the research efforts. It also appears that no manuscripts have been submitted for publication or are close to completion.

Dr. Renee Reams and Dr. Novak are certainly capable of providing leadership for the ARCH program. It appears that several of the FAMU faculty and research staff has taken advantage of the opportunity to perform mini-sabbaticals at Wayne State. Thus, the administrative and planning core has been successful in ensuring the transfer of certain cell and molecular biological techniques to FAMU. This is seen as a strength. Unfortunately, it was not felt that this brief eight-week stay at Wayne State provided enough time for the mentoring needed to carry the studies to fruition and publication. Although the FAMU-WSU scientists have attempted to use various means of communication, it appears that the geographical distance is a very formidable obstacle and communication is not optimal. Support mechanisms for investigators are in place, both advisory committees are staffed, and have met and provided recommendations. However, it was disappointing that the participation of the External Advisory Committee in the evaluation and selection of the new pilot projects can only be described as meager at best. It is also somewhat surprising that this committee did not meet prior to the mid-program evaluation. It was not clear if this meeting was not held due to lack of planning or lack of commitment from the External Advisory committee. On a positive note, the Senior Scientific Advisor is engaged, and providing support to the PI and investigators. Several recommendations were made concerning the Administrative and Planning Core, which included primarily an expansion of persons to provide a mentoring role. Specifically it is recommended that the PI and co-PI should affiliate with either the National Council of University Research Administrators or the Society of Research Administrators http://www.srainternational.org/newweb/default.cfm as a means of professional development and networking among individuals experienced in grant administration who can mentor individuals on relevant aspects of ARCH activities. Also it is recommended that there be an expansion of the pool of external peer reviewers (e.g. Florida Moffitt Cancer Center) to ensure objective and thorough written critiques, and possible expansion of research collaboration. Overall, the Administrative and Planning Core is rated as satisfactory.

There were several weaknesses revealed during the site visit in both of the research projects. The interaction between the FAMU-WSU scientists on both of the research projects appears to be limited. For the ARCH program, this is unsatisfactory. Additionally, the productivity on both of

these projects was also limited. Nevertheless, the scientific presentations for both projects were disappointing and this is an area that needs substantial improvement. A significant change in the type of interactions across the two schools is needed to achieve the goals of the ARCH program. A marked improvement in the depth and breadth of the collaboration and mentorship must take place to bring these interactions into the spirit of the ARCH Program.

Two pilot projects have been completed during the initial phase of this ARCH program. Dr. Thomas presented very interesting data at the site visit. This pilot project proposed to study the role of phase I and phase II metabolism in the generation of reactive metabolites of PhIP in breast tissue that might cause an increased risk of breast cancer. Overall, progress in this pilot project is deemed excellent. The PI is encouraged to develop further the more promising aspects of this work with view to a publication and to a R01 grant submission.

Dr. Gragg's 2.5-year pilot project proposal was included in the original ARCH grant application. At that initial review this project was rated as excellent. The hypothesis proposed by this pilot project was that the Ah receptor inhibits androgen dependent cellular proliferation by regulating RB activity in human prostate carcinoma LNCaP cells. Significant problems in interpretation of data were apparent at the site visit. Dr. Kocarek realized that he could not provide expertise in the interpretation of flow cytometry data. At the site visit, Dr. Kocarek indicated that he and Dr. Gragg sought and received assistance in the analyses of the data in question from a colleague at Wayne State University, Dr. John Reiners, a member of the Wayne State EHS Center with recognized expertise in the interpretation of flow data. While this acknowledgment of inexperience is viewed as a positive from the standpoint of providing mentoring, there are significant concerns about the interpretation of Dr. Gragg's data and the recommendation was made that additional input in the interpretation of this data is necessary before it will can published or used as the basis for a grant application. Unfortunately, the overall progress in this pilot project is deemed unsatisfactory. Data from this work were presented to two AACR meetings and are thought to be at the stage of preparation for publication; however, there are major problems in data interpretation that might preclude publication.

The process for identification of new pilot projects included appropriate advertising at FAMU, external review of the applications from both the External Advisory Committee and faculty at WSU. Two projects have been identified and were presented at the site visit. The investigators for both projects made satisfactory presentations at the site visit. It is extremely important that appropriate mentors be identified for them both at FAMU and at WSU. Also, it is crucial that communications be improved so that the necessary mentoring will occur. This portion of the ARCH program is viewed as satisfactory.

The original grant application described a single Cell Culture and Molecular Methods Core with 2 components, but it has evolved as 2 separate cores, one for cell culture and flow cytometry, the other for molecular methods. These core facilities appear to be a success, and meet the mission of the ARCH program to create research infrastructure at FAMU. A strategy for continued support of this facility beyond the period of ARCH funding has not been described; this is an effort deserving of institutional support. In addition, a cost-sharing mechanism with investigators who use the facility should be considered.

The institutional commitment of FAMU to the ARCH Program is excellent. The University has instituted a policy that provides release-time to all faculty members with external funding according to the percentage of effort approved in the contract or grant. Faculty members are to be relieved of normal teaching responsibilities in an academic term commensurate with the amount of release-time generated on a sponsored project(s). Specific arrangements are negotiated when the generated release-time is less than one course load or commences after

the start of an academic term. Upon the recommendation of the ARCH EAC FAMU has instituted a new policy that provides faculty members with 15% of recovered indirect costs and provides 10% to departments. As part of their commitment to research across the entire campus, in addition the return of 25% of the administrative costs the University has begun to make travel awards and provide lap top computers. The ARCH program has held grant writing workshops and the institution will provide funds to allow PI's to attend grant writing seminars. The administration has also implemented various approaches to mentor junior faculty so that they can become seasoned investigators. These are recently implemented policies that, in part, have been developed in response to suggestions from the ARCH EAC. This is a positive outcome for the ARCH program. FAMU has been building research facilities. Many of the investigators in the ARCH program have space in the new facilities. In addition, space was provided for the ARCH Cell Culture Facilities. It is recommended that the Molecular Biology facility, which is currently located in an individual's lab space, be given separate space. The institutional commitment made by FAMU on behalf of ARCH is rated as satisfactory.

Background

Florida A&M University (FAMU) is a Minority Serving Institution (MSI), which is partnered with Wayne State University (WSU), a Research Intensive University (RIU) for this Academic Research Cooperation in Environmental Health (ARCH) program. It began as the State Normal College for Colored Students in 1887. In 1891 it received funding under the Second Morrill Act for agricultural and mechanical arts education and became Florida's Land Grant Institution for African-Americans. Its status was elevated to University in 1951.

Support of the university is essential to the success of the ARCH program. In the mid 1990s FAMU developed a five-year plan to expand its research program and seek out opportunities to obtain external funding. It currently offers numerous Ph.D. programs. In an effort to increase research capacity, within the past year the administration has hired a new Vice President for Research who has restructured the Office of Sponsored Research. Over the past year the University has surpassed the $100 million mark for external funding.

Administrative and Planning Core

R. Renee Reams

Dr. Reams earned the PhD degree in biochemistry (1984), Brigham Young University and completed a postdoctoral experience at the University of California, LA in 1986. She has experienced one faculty appointment prior to joining FAMU in 1991, rising to associate professor (tenured) in 1999. She has been the Program Administrator, HRSA Centers of Excellence Grant since 1992.

In 1992, she became the program administrator of the HRSA Centers of Excellence Grant, which remains in force.

She was the recipient of an NIH/NIEHS minority scientist award (1995-2000) and has participated in a two-part FASEB grant-writing seminar (2000).

She concluded a four-year experience, research development and training in molecular biology, WSU in the year 2000.

Dr. Reams is a reviewer, Journal of Pharmacology and Experimental Therapeutics. And, she has reviewed articles for Gene and Mutation Research, and Canadian Journal of Physiology and Pharmacology.

Six publications are listed since 1998, with three being published in Research Communications in Molecular Pathology and Pharmacology.

She has ten refereed publications, and one submitted to date, one below the number required for promotion to full professor. Six publications have been recorded since 1998.

Dr. Reams is quite capable of providing leadership for the ARCH program.

Raymond F. Novak

Dr. Novak is prepared, experienced and desirous of FAMU learning molecular technology, collaboratively publishing with WSU in tier-one journals, enhancing the research program and writing proposals involving both institutions.

While actively engaged as a member of two FAMU advisory groups, Research Centers in Minority Institutions and the Minority Biomedical Research Program, the level of focus and oversight in regards to the ARCH initiative appears to be less than optimal. The full potential of inter-institutional collaborative research is not presently being fully realized in the Advanced Research Cooperation in Environmental Health Sciences funded project.

FAMU investigators have spent summers at WSU learning techniques. In some instances, graduate students or technical personnel also attended. This arrangement has not fully achieved its potential, as FAMU investigators are perceived to realize slower progress on returning to address campus responsibilities.

Neither Dr. Reams nor Novak have been exposed to the programming of the National Council of University Research Administrators [NCURA], the Society of Research Administrators [SRA] programming or persons experienced in research relationships between research and undergraduate institutions. Such exposure will prove to be instructive in inter-institutional communications, differences in campus cultures and pressures and best practices.

Communications

Communications occur in many ways between Florida A&M University (FAMU) and Wayne State University (WSU). E-mail and telephone (land and cellular) have proven to be the optimal methods of communications, between campus visits, or engagements at various meetings. FAMU personnel can reach a WSU colleague in the office/laboratory by phone with fidelity.

Electronic communications have been previously engaged, and currently FAMU is equipped for such. WSU will require additional renovations to employ this technology.

Grantsmanship Workshop Deliverables

FAMU investigators participated in WSU and other grant writing sessions as a means of sharpening writing skills. Basic science faculty reports directly to the Division Director whose annual evaluation isolates deficiencies, and strengths. Investigator involvement in efforts aimed at grantsmanship skill development did not directly involve the supervisor or attach to the expectation for a deliverable.

A best practice for faculty participation in a grantsmanship workshop is the high expectation/ requirement for submission and evaluation of the basic concept for a proposal. The services of

an editor should be a consistent feature in the review of the concept paper and proposal. And, the investigator, Division Director and ARCH PI should agree on a declared and mutually acceptable submission date for the R01 proposal.

Organizational and Research Facilities, Commitments

As of November 2003 FAMU moved into the new Pharmacy Building, equipped with a distant learning laboratory, computer lab and 12 research labs that are soon to be occupied. ARCH investigators and laboratories are located in the old or Dyson Pharmacy Building and the Frederick Humphries Science Research Facility.

A major indication of changes in the research culture of FAMU is the allocation of recovered indirect cost dollars. This major, progressive step in developing the research environment allows for the return of 15% faculty member and 10% to department or dean. This development was in response to an External Advisory Committee (EAC) recommendation.

On the appointment of the Vice President for Research, Dr. Phyllis Gray-Ray, the Division of Research was reorganized to better meet the needs of the community. One positive outgrowth of the new administration is the creation of eight new committees designed to provide constituent input to the Division. The Faculty Research Advisory Committee [faculty concerns, review of internal proposals, research planning] and the Research Council [policy matters] are both chaired by the Vice President. This organizational arrangement will not serve the institution well as members will be reluctant to objectively craft agenda and provide maximum engagement when being led by the highest ranking officer to which it reports, and may criticize. A best practice is to allow such bodies to elect a leader from among its ranks.

The Division of Research recently implemented a Research Incentive Award program which entrails an annual $5,000 cash award to two or three faculty who have demonstrated research excellence. Moreover, a cash award of $5,000 will be added to the base salary of the faculty member who receives a R01 grant award.

These incentives and other support services aided FAMU in achieving its $100 million external awards goals in advance of the target date. The College of Pharmacy generates about one-third of this funding level. Obviously, the college and the university have evolved as a grant-seeking environment with a high rate of success.

The College of Pharmacy provides start-up funds for the purchase of small equipment and pilot project support for new faculty who meet specified qualifications.

Advisory Committees

The Internal Advisory Committee is comprised of ARCH principle investigators, the Senior Scientific Advisor, and five FAMU and WSU investigators. The committee meets quarterly, and is active in guiding the program. A meeting summary, but not minutes, was provided.

The External Advisory Committee (EAC) is comprised of five members of significant standing in the scientific community. Members have made several recommendations, summarized in submitted documents. Many recommendations have been addressed, or placed under consideration.

The EAC met June 3-4, 2003 that indicates the next annual meeting would likely occur in June 2004. That meeting was to also provide a critique preparation for mid-program evaluation. Relevant recommendations are included in submitted documents.

Given the late 2003 notification of the mid-course evaluation date, it is surprising that the EAC was not engaged for a timely and more focused meeting, if not a mock site visit in calendar year 2004. This type of EAC engagement would have allowed critical questions to be asked, presentations to be polished beyond the evident level and solutions identified for existing challenges.

Senior Scientific Advisor (SSA)

Dr. K. Redda, the current SSA is an active participant in the Internal Advisory Committee, and has been engaged in investigator preparation of grant applications.

Postdoctoral Training of MSI Researchers

Dr. Rearms, ARCH Program Director received postdoctoral training prior to becoming a faculty member. Similarly, two more [Jain, Heiman] ARCH researchers have postdoctoral training. Five of the researchers were hired since 1995, indicating a clear direction towards a stronger research environment.

ARCH: Interdependence of Wayne State and Florida A&M Universities

Dr. Novak mentioned a desire to assist FAMU with the further development of its research potential in terms of molecular biology, and collaboration in refereed publications and proposal submissions.

Wayne State did not present a well thought out goal, or procedure for availing itself of the tremendous opportunity of a well-developed, broad based articulation with a Historically Black University. WSU has not set forth a plan for attracting FAMU undergraduate science majors to its recently funded NIEHS training program in molecular and cellular toxicology.

A positive step has been the granting of Environmental Health Sciences Center Associate member status, which allows full access to staff and Center facilities. As Visiting Scientists, FAMU investigators are granted access to university libraries, housing and other resources. This trend has not progressed to an adjunct or similar appointment of investigators from either institution on the collaborating campus.

As an RCMI institution FAMU has Ph.D. degreed research associates receiving postdoctoral training. This population is not being aggressively recruited for faculty positions at WSU.

The FAMU College of Pharmacy has graduated over 60% of the African-American Ph.D.s in the pharmaceutical sciences in America. While in training, these students are available for summer internships. Given the involvement of graduate students in ARCH research, the establishment of thesis parts arrangements would be a logical outcome. WSU has not published plans for recruiting these graduate students to faculty or postdoctoral training.

WSU does recommend that FAMU investigators invest, along with graduate students, a minimum of six months in sabbatical as a means of increasing manuscript productivity.

Recommendations

1. The PI and co-PI should affiliate with either the National Council of University Research Administrators http://www.ncura.edu/resources/default.htm or the Society of Research Administrators http://www.srainternational.org/newweb/default.cfm as a means of professional development and networking among individuals experienced in grant administration who can mentor individuals on relevant aspects of ARCH activities. A specific effort to learn from others who have experienced collaboration in research between undergraduate and research intensive institutions should be mounted.

2. Best practices and experiences gained through ARCH should be presented and/or published through Society of Research Administrators or National Council of University Research Administrators

3. The basic science Division Director should schedule semi-annual or even more frequent engagement in mentoring faculty towards an increased number of refereed publications in collaboration with ARCH leadership and WSU mentors.

4. Progressive changes in the research culture to affect a primary focus on R01 funding leading to a mix of investigator initiated and targeted funding. Redefinition of faculty job descriptions would allow reflection of a new level of productivity expectations and a basis for evaluation. Changes will require the full involvement of the affected faculty, division directors, deans and the Provost.

5. Expansion of the pool of external peer reviewers (e.g. Florida Moffitt Cancer Center) to ensure objective and thorough written critiques, and possible expansion of research collaboration.

6. Enhance the role of the EAC proximal to mid-course evaluation or proposal submission in the critical evaluation of productivity and progress of all parties.

7. Bring a more effective structure to PI-to-PI communications to include progress of pilot and research projects, publications, plans for proposal submission and mentoring.

8. Wayne State University is strongly encouraged to follow through on its desire to develop a formal affiliation agreement with Florida A&M University that will strengthen collaboration on proposal development and submission, publications in leading journals, growth in the application of molecular biology technology and research. An affiliation will allow for recruitment of undergraduate students, Ph.D. graduates and post doctoral trainees and joint appointment of faculty on each campus.

9. As the direct supervisor to ARCH investigators, the basic science Division Director should be added as a voting member to the Internal Advisory Committee.

10. Consistently engage editorial services in preparing progress reports, slides, proposals and manuscripts.
11. FAMU PI and Senior Scientific Advisor recommended and Division Director enacted adjustment of faculty committee and student advisement duties to appropriate levels given research time requirements.

Rating
Support mechanisms for investigators are in place, both advisory committees are staffed, and have met and provided recommendations. The Senior Scientific Advisor is engaged, and providing support to the PI and investigators. Laboratories have been established and are generating data. The Administrative and Planning Core is rated as satisfactory.

Process for New Pilot Projects

Critique 1
The process for the selection of new pilot projects included a University-wide solicitation of letters of intent and abstracts, a screening of abstracts for "fit", development of proposals with external

review, followed by NIEHS review and notification. Six projects were submitted initially however for varying reasons only two projects made it through the selection process. Although it was originally planned that the investigators for the selected pilot projects would have the opportunity to participate in an eight-week summer research training program at WSU in the summer of 2004, at the time of the site visit only one project had made it through the external review and had been submitted to Dr. Tyson. Consequently, the new pilot project investigators will not be able to attend the training program at WSU this summer.

A presentation was made by each of the new pilot project investigators. Both presentations were satisfactory and it appears there is great enthusiasm by the new investigators. Because one of the new pilot projects involves keratinocyte organotypic culture, there was some concern that appropriate expertise would not be available at WSU. However, Dr. Novak informed the review committee that Drs. Kocarek and Runge-Morris had just submitted a proposal involving keratinocytes and that they would be capable of mentoring Dr. Sachdeva.

Overall, the process for new pilot projects appears to have been successful because two projects have been identified. During the process, the abstracts were sent to the members of external advisory committee. It was discouraging that only two of the six members of the external advisory committee returned evaluations to Dr. Reams.

Rating
This portion of the ARCH program is viewed as satisfactory.

Critique 2
The seven-point outline describing the selection of new Pilot Projects contained the appropriate components for the competition for pilot project awards, including University-wide advertisement and call for abstracts. However, the resulting peer-review process regarding the applications for pilot projects was less than ideal. The ARCH External Advisory Board was chosen to serve as the peer-review panel for the applications, but only two of five members responded with reviews. Whether this lackluster response resulted from poor scheduling of the pilot project review or disinterest of some Board members was unclear. Given the critical importance of peer review in any competition for funding, firm commitments from an appropriate number of reviewers should be obtained prior to the competition, regardless of whether individuals other than those on the external review committee must be sought.

Potential projects were forwarded to WSU for appropriateness of mentoring, and Dr. Kocarek then provided additional interaction and feedback regarding goodness-of-fit in the potential mentoring and training opportunities at WSU. This interaction with Dr. Kocarek and other faculty at WSU was seen as critical to the success of the pilot project program, and appears to have had a positive outcome. The process has resulted in two projects for the second cycle that appeared to have high likelihood for success.

Rating
The New Pilot Project Process is considered satisfactory.

Critique 3

The progress report describes six pilot projects, and a process for review and selection of awardees that would start funding in summer of 2004. Two pilot projects will be funded. The pilot investigators made presentations at the Mid-Program Evaluation visit. It is not clear how they will interact with mentors at WSU.

The process is said to involve peer review of new pilot project proposals by members of the ARCH program and of the external advisory committee. Recommend written reviews should be generated and forwarded to the pilot investigators and to NIEHS. The criteria for scoring proposals were not described.

Recommendations

1. The process of identifying a mentor/collaborator at WSU needs to be re-evaluated and corrected. Mentors should also be identified at FAMU.
2. There should be a process to request evaluation of the pilot program from currently and previously funded pilot investigators. This could help the Program PI enhance the Pilot Project Program.
3. There should be a process to evaluate the pilot projects every year, and a process to discontinue funding for inadequate progress.

Rating

The New Pilot Project Process is considered satisfactory.

The PIs of all research and pilot projects were asked to provide information on their presentation and publication record. Below is the summary of the information that was provided.

Presentation/Publication Record by Project						
	Scientific Presentations	Papers Published in Peer-reviewed Journals	Papers Published in Proceedings	Papers In Press	Published Abstracts	Submitted/ In Prep
Res. Proj. 1	0	0	0	0	1	1
Res Proj #2	0	0	0	0	0	1
Pilot Proj #1	0	0	0	0	1	1
Pilot Proj #2	2	0	0	0	3	1
CellCulture/ Molec. Core	3*	0	0	0	3*	2
Flow Cytometry Core	3*	0	0	1	3*	1

* Used both facility cores

As the purpose of the ARCH program is to develop the research capacity at the MSI, it is important to see what progress has been made in the submission and award of new grant

applications. Therefore, the PI of each research and pilot project was asked to provide a list of all grant applications that have been submitted as well as their current status.

Grant Applications		
Submitted To	Grant Title	Award
RCMI G12RR03020 Active 8/13/03	Molecular Biology Research Activity; **PI: Thomas)**	$2,444,893
RCMI G12RR03020 Active 8/13/03	RCMI **Sub-proj (Thomas)**: Role of Gene Expression in Breast Cancer Prevention by Diallyl Sulfide	$ 241,217
NIH 1P20MD0050101 Active 9/30/03	FAMU and Harvard Center for Health & Health Care (To address environmental pollution and health disparities in Quicy, FL and enhance environmental health science research capabilities – Research Core; **Gragg is co-PI and has subproject**	$ 694,088
NOAA 40GENF20027278 9/10/03 WC13F03SE0669 Active 8/1/03	South Florida Ecosystem Restoration Interdisciplinary Science Participation Plan (To expand sampling for PAH and photoproducts in Everglades and address environmental justice in South Florida); **PI: Gragg**	$ 90,000
DOD W81XWH010326 2/12/04 (Active)	FAMU and H. Lee Moffitt Cancer Center HBCU Collaborative Partnership Training Award; Prostate Cancer Training Program. (Micro array Comparison of Prostate Tumor Gene Expression in African American Men and in Caucasian Men: A Feasibility Study.) Faculty Development Award; **PI: R. Reams**	$ 40,000
NIH (R03) (Pending)	Inhibition of PhiP Bioactivation by Diallyl Sulfide; **PI: Thomas**	$ 144,100

***Program note**: The RCMI award, while not a targeted grant program for ARCH, is an NIH grant that was submitted and awarded to ARCH investigators at FAMU. A large component from a P20 award from NIH in collaboration with Howard Hu was awarded in September 2003. [end note]*

Research Project #1 - *Melissa Runge-Morris, PI*
Environmental Intracrinology of Breast Cancer

Critique 1

This project is based on the hypothesis that estrogen sulfotransferase (SULT1E) and cytochromes P450 CYP1A2, CYP2B6 and CYP3A4 are expressed and tightly regulated in MCF10A breast epithelial cells, with each gene under the transcriptional control of a distinct set of trans-acting factors, and that these enzymes represent integral components of the breast epithelial estrogen intracrinology machinery. The investigators contrast MCF-10A as representing normal breast epithelial cells with MCF-7 as representing breast cancer cells in their model of environmental intracrinology of breast cancer. They argue that MCF-10A cells are estrogen-receptor (ER)

negative, and as such represent a more normal phenotype, since most normal epithelial cells are ER-negative. However, the differences in gene expression between MCF-7 and MCF-10A may be largely due to their divergence in the differentiation pathways of mammary epithelial cells and not necessarily due to genetic changes related to carcinogenesis

Progress on Aim 1 (Determine the molecular basis for differential expression of SULT1E in MCF-10A and MCF-7 cells) was reported in that a cDNA fragment corresponding to 5'-flanking region of the SULT1E1 gene was cloned and a series of deletion constructs was prepared to analyze SULT1E1 promoter activity. These reporter luciferase constructs showed activity in both MCF-10A cells, in which the endogenous gene is active, and in MCF-7 cells, in which the endogenous gene is silent. It is thus not presently known what molecular mechanism is responsible for the differential regulation of SULT1E1 in MCF-10A and MCF-7 cells. Differential DNA methylation is not thought to be involved based on the absence of appropriate CpG sites. Motif analysis suggested the presence of response elements for nuclear factor Y and several other transcription factors, but no experimental data were presented to suggest a role for a specific transcription factor in the regulation of SULT1E1 expression or that might be responsible for the differences in SULT1E1 expression between MCF-10A and MCF-7 cells.

Recent studies on the series of cell lines derived from *ras*-transformed MCF-10A cells showed decreased SULT1E1 expression in the more tumorigenic cell types. The comparison of these lines offers the advantage that SULT1E1-expressing and -nonexpressing cells were derived from a single cell type. The changes in transcription factor expression responsible for the loss of SULT1E1 expression in these cells may be more readily apparent than with the MCF-10A/MCF-7 comparison. While these data and observations on SULT1E1 expression are interesting and represent a framework for future studies, a complete story worthy of publication was not presented.

Progress on Aim 2 (Define the expression of CYP1A2, CYP2B6 and CYP3A4 in MCF-10A breast epithelial cells) was reported in that methods for real-time PCR and western blot analysis have been developed for analysis of the CYP mRNAs and proteins. It was reported that CYP1A2 protein is not significantly expressed in MCF-10A cells, and therefore will not be studied further. No data on CYP2B6 or CYP3A4 expression was presented. In the initial peer review of this project, the concern was raised "as to whether the P450 proteins will be expressed at detectable levels, because if the are not, much of the study is of questionable relevance." At the midpoint of the project, this concern remains. It seems as though the Western blots for CYP protein expression and the assays for the probe activities of CYP2B6 (S-mephenytoin N-demethylase) and CYP3A4 (testosterone 6beta-hydroxylase) should have been completed by this juncture. The estrogen hydroxylase activity of CYP2B6 is very low and the Km for estrogen hydroxylation by CYP3A4 is quite high, 50 micromolar (Lee et al., 2003; Endocrinology 144:3382-98); these enzymes would therefore have to be expressed at high levels for them to significantly impact estrogen homeostasis in a manner consistent with the central hypothesis of the project.

No progress on specific Aim 3 (To determine the molecular basis for the breast epithelial cell-specific expression of CYP1A2, CYP2B6, and CYP3A4) was reported.

There has been limited progress on Specific Aim 4 (To determine, through the use of microarray analysis, whether the alterations in molecular phenotype of MCF-10A cells that are produced following genetically-induced alterations in CYP1A2, CYP2B6, CYP3A4 or SULT1E expression are solely attributable to effects on cellular levels of bioactive estrogen), as MCF-10A-dervied cell lines stably over- or underexpressing these enzymes have not been obtained. Experiments with the Tet-Off and Tet-On systems were apparently unsuccessful, and there has been a shift in technology to the adenovirus system for overexpression of the CYPs and SULTT1E1. Dr. Jain of the

Molecular Methods Core Facility at FAMU appears to be doing the majority of the work on cloning of adenoviral expression constructs for the overexression of CYPs and SULTs for the ARCH program. It was not indicated how Dr. Jain's work at FAMU is currently interactive with or supportive of Research Project 1, or whether there will be a duplication of effort at WSU on CYP and SULT overexpression.

Rating
In summary, while some progress has been made on Aim 1, progress on Aims 2, 3, and 4 has been modest at best. The lack of published papers and submitted manuscripts from this project is a significant concern. Progress must therefore be considered unsatisfactory.

Critique 2
The stated hypothesis of this proposal is that various phase I and phase II detoxification genes are tightly regulated in MCF10A breast epithelial cells and that the corresponding enzymes are integral components of the intracrinology of breast epithelial cells. Progress in this project is expected from the integration of Dr. Ron Thomas to the research. From the Report, it is difficult to determine what, if any, was Dr. Thomas' contribution to the progress. During the site visit, it was made evident that Dr. Thomas was not a participant in this project, but that a new hire at FAMU was much involved in the development of biological reagents pertaining to this project.

The first specific aim proposed to determine the molecular basis for the differential expression of the sulfotransferase gene SULTE1 in MCF10A (non-neoplastic breast epithelium) and MCF7 (breast carcinoma). Deletion analyses identified the minimal core promoter needed for basal expression. Microarray analyses indicate that SULT1E becomes silenced in breast epithelial cell lines with increasingly malignant phenotypes. The report gives no clear sense of what relevance these findings may have to the purpose of this aim, which shows little progress in the 2.5 years of the grant.

The second specific aim proposed to define the expression (sic) of the cytochromes P450 CYP1A2, CYP2B6 and CYP3A4 in MCF10A cells. The main finding of this aim has been that it was CYP1A1, not CYP1A2, the CYP1A family member expressed in these cells. This is very minimal progress, particularly if it is taken into account that it is a well-known fact that expression of CYP1A2 is extinguished in tissue culture cells, which should have precluded the need for the test to begin with.

There has been no work done in aims 3 and 4.

Rating
Overall, progress in this research project is deemed unsatisfactory. Investigators at the RIU and MSI need to come together and set specific goals and milestones for this project to advance at a reasonable pace. To have two or three FAMU investigators visit WSU for a few days or a couple of weeks of the year is clearly insufficient to insure an acceptable rate of progress.

Program note*: Regarding the reviewers' concerns about research progress associated with specific aims 2 through 4, it should be recognized that each of these specific aims requires the development of molecular reagents and techniques, which represents the major hurdle for the completion of the aims. At the Mid-Program Evaluation site visit Dr. Runge-Morris discussed the efforts that had been made in developing the reagents and techniques required, as well as the directions in which the research would progress now that the working methods for aims three and four have been developed. [end note]*

Research Project #2*: Thomas Kocarek, PI*
Environmental Estrogen Effects On Prostatic Phenotype

Critique 1

This Research Project was not part of the original ARCH application submitted in October 2000. It was submitted to Dr. Tyson, the ARCH Program Director at NIEHS, in August 2001, one month prior to the start of funding, to replace the original RIU Research Project #2 (PI, Dr. Cornelis Elferink, "Ah receptor action and apoptosis [in liver]"), which was reviewed and rated by the study section as excellent. Dr. Elferink has left WSU, the RIU. Dr. Elferink was to have been mentor for Dr. Richard Gragg, PI of MSI Pilot Project #2 ("AhR modulation of androgen dependent prostate cell growth").

It appears that the application by Dr. Kocarek was not peer-reviewed, as there is no summary statement to indicate the basis on which it was accepted as a replacement for Dr. Elferink's project. It was not even reviewed by the External Advisory Committee appointed by WSU and FAMU, because the committee had not become functional prior to grant funding. In the opinion of this reviewer, it should not have been funded. Dr. Kocarek's proposal was "specifically designed to provide Dr. Richard Gragg of FAMU with a vehicle for learning modern techniques in molecular and cellular biology that are highly applicable to his ARCH pilot project [on AhR modulation of androgen dependent prostate cell growth]." This is poor justification for a research project by a member of an RIU. Dr. Kocarek's long-term research program has focused on hepatic P450 gene expression, and there is no evidence that he has any expertise in the area of prostate biology or the Ah receptor. Peer review would have criticized the lack of a hypothesis, and would have noted that Dr. Kocarek's lack of expertise in the subject of his proposal would severely undermine his ability to provide effective mentoring of Pilot Project Investigator Richard Gragg.

Dr. Kocarek's proposal does not address a significant research question, and it lacks a worthwhile hypothesis. The stated hypothesis is that treatment of LNCaP prostate cancer cells with isomers of DDT produces unique profiles of concentration-dependent effects attributable to multiple mechanisms of action. The basis for this hypothesis is the PI's stated goal of designing experiments that utilize techniques required for Dr. Gragg's pilot project.

Dr. Kocarek's proposal has 3 specific aims. The first aim is to define the concentration of DDT isomer that produces the least effect (LOEL) on LNCaP cell molecular phenotype (measured by microarray analysis of mRNA changes), on signal transduction pathway activities (measured by transiently transfecting pathway-sensitive reporter plasmids), and on cell proliferation (measured by flow cytometry). Experiments to date have been the use of a 12,000-gene microarray to analyze RNA in LNCaP cells treated for 24 hr with various concentrations (1 nM to 1 M) of the 2 DDT isomers in standard culture medium, vs. in medium supplemented with 100 nM DHT or 100 nM estradiol. This experiment was done in triplicate, consuming 90 Affymetrix GeneChip's. The stated results are that "overall the variability among triplicates was found to be too great to permit the detection of many gene expression differences". The next step was to repeat the experiment using only a single concentration of DDT (high or low? not stated), and a different microarray that contains 41,000 gene transcripts. The PI has not considered the possibility that the results of the first experiment may be 'negative' (1) because of a lack of sensitivity of the microarray assay to detect small changes, or (2) because DDT at the concentrations tested in fact have no significant effect, or (3) because the treatment duration was not appropriate (a single time point was chosen for practical reasons).

In other progress to date, the PI also reports no effect of the different concentrations of the DDT isomers on cell cycle distribution, as measured by flow cytometry after 3 days of treatment. The

plan is to now treat LNCaP cells for 4 weeks. Again, the PI has not considered the possibility that these experiments point to a lack of effect of DDT on LNCaP cells, and that they could account for the lack of effect on RNA levels. Thus, two independent approaches have failed to demonstrate an effect of DDT on LNCaP cells, and further investment in the planned experimental strategy cannot be justified. However, the PI remains committed to the original plan. This lack of thoughtful analysis does not serve the goals of the ARCH program.

Dr. Kocarek presented new data at the Mid-Program Evaluation visit. He concluded that long-term culture of LNCaP cells in DDT led to increased susceptibility to activation of caspase-3 by HA-14, an activator of apoptosis. However, he also showed that long-term culture in DMSO [the vehicle control] had an even greater effect; his response to a question about this was to ignore that DMSO data. This is unacceptable performance by an established investigator and mentor.

Aims 2 and 3 were to have defined the contribution of ER beta and AR to the effects of DDT on LNCaP cells. In the absence of an effect of DDT, aims 2 and 3 cannot be justified.

To date, no scientific presentations have been made, no abstracts or manuscripts have been written, and no additional grant applications have been generated.

Recommendation/Rating
Discontinue funding of Dr. Kocarek's Research Project. The basis for this recommendation, described above, can be summarized as: lack of hypothesis, poorly designed experimental strategy, lack of thoughtful data analysis, lack of productivity, and failure to effectively mentor Dr. Gragg. Moreover, Dr. Kocarek's 5-year proposal was designed to 'dovetail' with Dr. Gragg's 2.5-year Pilot Project; however, the next round of 2.5-year pilot projects [Pilot Project Investigators were presented at the mid-program evaluation site visit] are unrelated to the subject of Dr. Gragg's research interests, and Dr. Kocarek has no plans to redesign his research proposal [which would require peer-review even if it were being considered]. Therefore, the stated goals of Dr. Kocarek's research proposal cannot be used to justify continued funding.

Critique 2
This research project proposed to study the profile of concentration-dependent effects resulting from the treatment of the prostate carcinoma cell line LNCaP with the environmental estrogens p,p'-DDT and o,p'-DDT and to determine the lowest observable effect levels (LOEL) for these compounds using global gene profiling techniques.

The first specific aim proposed to study modifications of molecular phenotype, signal transduction pathway activities and proliferation as measures of LOEL of the two compounds indicated. The report indicates that one set of high-density microarray experiments was done, treating the cells with p,p'-DDT or o,p'-DDT for 24 hours in the absence or presence of the dihydrotestosterone analog R1881 or beta-estradiol. Experiments done in triplicate reportedly led to such variability that no conclusions could be made. No differences were observed in parallel experiments designed to analyze differences in cell cycle progression.

No progress is reported for specific aims 2 and 3.

No presentations, publications or additional funding has been generated from this research project.

Rating
Overall progress in this research project is deemed unsatisfactory. Although the declared PI is a member of the RIU, there seems to be little direction provided by the RIU investigators on the

successful accomplishment of the research aims. For this research to accomplish its goals there is a pressing need that the WSU scientists take a more proactive role.

***Program note**: In the review of Research Project #2, the reviewers concluded that the project is not worthwhile and cannot be successful. This project addresses the issue of whether, and by what mechanism(s), organochlorine pesticide treatments (using DDT as the model compound) alter the behavior of androgen-responsive prostate cancer cells (using LNCaP cells as the model cell line). At the Mid-Program Evaluation presentation, Dr. Kocarek listed five epidemiological studies published in 2003 and 2004 that support an association between prostate cancer and pesticide exposure. As NIEHS has an interest in the effects of organochlorine pesticide exposure on human health, program staff considered this to be an acceptable replacement project for the one that was withdrawn.*

Several statements are made that challenge Dr. Kocarek's competence to direct the research project. Although Dr. Kocarek does not have a publication record in prostate biology and is not an expert in cell cycle biology, Dr. Kocarek does have a publication record in the regulation of gene expression by organochlorine pesticides and nuclear receptors. He is therefore well grounded in two of the essential aspects of the research project (i.e., effects of DDT and roles of estrogen and androgen receptors). Furthermore, to add support in the area of cell cycle biology, Dr. John Reiners (Institute of Environmental Health Sciences), a recognized expert in the role of the Ah receptor in cell cycle regulation, has served as a consultant on the project since its inception. [end note]

Pilot Project #1 - *Dr. Ronald Thomas, PI*
Breast bioactivation of PhIP: Implications for Carcinogenesis

Critique 1

Major progress on the studies of Aim 1 [To demonstrate the bioactivation of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) by CYP1A2 and SULT1E] is evident in that the difficult technique of ^{32}P post-labeling is used now used routinely, and the technique has been used to show the formation of DNA adducts in MCF-10A cells after exposure to N-OH-PhIP or PhIP. However, it has yet to be determined which enzymes catalyze the metabolic activation of PhIP in MCF-10A cells. The effects of the SULT1E inhibitor, estrone, and the CYP1A2 inhibitor, furafylline, were not reported; however, alpha-naphthoflavone, an inhibitor of both CYP1A1 and CYP1A2 (Shimada et al., 1998; Chem. Res. Toxicol. 11, 1048-1056), was shown to reduce adduct formation. Enzyme activity determinations and protein expression studies would appear to be necessary in addition to the inhibitor experiments to justify the proposed over-expression experiments with selected CYPs and SULT1E1. A portion of the original hypothesis was disproved in that it was reported that CYP1A2 is not expressed in MCF-10A cells. Is the evidence for SULT1E1 involvement suspect as well? Could N-acetyltransferase (NAT) be involved in N-OH-PhIP conjugation rather than or in addition to SULT1E1? Since SULT1A1 also acts on N-OH-PhIP, might it be involved? Could CYP1A1 rather than CYP3A4 or CYP2B6 catalyze the N-hydroxylation of PhIP?

No results were reported for Aim 2 (Demonstrate the activation/lack of activation of PhIP in MCF-10A genetically engineered to overexpress and/or underexpress CYP1A2 and SULT1E) or Aim 3 (Demonstrate alteration in the molecular phenotype of MCF-10A cells by PhIP treatment such that they have increased/decreased ability to metabolically activate PhIP), due to the fact that the MCF-10A-derived cell lines overexpressing the CYPs and SULT1E1 to be developed in Research Project 1 have not been produced. However, interesting new data was presented on the formation of DNA strand breaks caused by PhIP exposure and the effects of inhibitors of DNA

repair on PhIP-induced DNA strand breaks. While no peer-reviewed research papers have resulted from this work, it is clear that considerable advances have been made and that publishable data has been produced.

Rating
Progress is considered satisfactory.

Critique 2
This pilot project proposed to study the role of phase I and phase II metabolism in the generation of reactive metabolites of PhIP in breast tissue that might cause an increased risk of breast cancer. Progress has been extensive in this project. The research shows that PhIP requires metabolism to cause DNA adducts in MCF10A cells. Because adduct formation is partly inhibited by ANF, metabolism is proposed to be partly dependent on the activation of CYP1A1. In fact, ANF is an antagonist of the Ah receptor, which might expand the number of P450s that may be involved in the metabolism of PhIP. Other conclusions, such as the concept that liver need not be involved in PhIP metabolism because breast cancer cells can do it, are very premature, since a first pass through the liver may quickly detoxify the compound, which might never be seen by the breast tissue.

Slower progress has taken place in the second aim, which proposed to clone the cDNAs of various P450s an sulfotransferases in vectors suitable for the analysis of PhIP metabolism in transfected cells. These experiments await the cloning of these cDNAs in adenovirus vectors.

Rating
Overall progress in this pilot project is deemed excellent. The P.I. is encouraged to develop further the more promising aspects of this work with view to a publication and to a R01 grant submission.

Pilot Project #2 – *Dr. Richard Gragg, PI*
AHR Modulation of Androgen Dependent Prostate Cell Growth

Critique 1
Dr. Gragg's 2.5-year pilot project proposal was included in the original ARCH grant application, and was rated as excellent. As stated by the reviewers, a strength of the proposal was the expertise and collaboration with Dr. Elferink, PI of a proposed Research Project at WSU. Unfortunately, Dr. Elferink left WSU, leaving the research project designed by Dr. Kocarek to fill this role. Originally, the pilot project was viewed as "a natural extension of and following logically from the observations and hypotheses presented by Dr. Elferink." Without Dr. Elferink's participation in the ARCH program, the appropriateness and feasibility of the pilot proposal become problematic. According to the initial review, "the major weakness was that, conceptually, it adheres itself too closely to the hypotheses developed by Dr. Elferink."

Because Dr. Gragg's expertise had previously been in the area of environmental justice, the reviewers recognized that success of the pilot project would depend heavily on Dr. Elferink's participation, and they expressed concern that an annual eight-week summer session spent in the mentor's laboratory at WSU might not be adequate training for Dr. Gragg. Only 10% of Dr. Gragg's effort was committed to this pilot project.

The specific aims of Dr. Gragg's pilot project were: (1) to determine whether the AhR can inhibit androgen dependent prostate cell proliferation by regulating G1 cell cycle progression, and (2)

to determine whether androgen dependent LNCaP cell growth can be regulated by controlling AhR function and the level of Rb protein. The project completion date is expected to be July 31, 2004.

Progress to date

In one series of experiments, the PI studied the effect of 24 hr treatment of LNCaP cells with androgen (R1881), TCDD (a ligand for the AhR), or both together, on cell viability (measured by an MTT assay) and cell cycle distribution (measured by flow cytometry). The prediction was that TCDD, via activation of the AhR, would inhibit androgen dependent cell proliferation, allegedly as reported previously by Jana et al, 1998 (reference not in list in original proposal). However, the PI was not able to demonstrate an effect of androgen on cell viability or on cell cycle distribution. TCDD at 0.1 - 10 nM also had no significant effect on cell viability, not by itself and not in the added presence of 0.1 nM R1881; 50 nM TCDD did decrease viability, both alone and together with 0.1 nM R1881, but this dose was not studied for its effect on cell cycle distribution or protein levels. A puzzling feature of the experiments is that the drug vehicle, DMSO, by itself, appears to decrease viability compared to medium alone, although it is not clear whether this effect is statistically significant. The PI should be concerned that an effect of vehicle may be masking an effect of the drug, and take steps to address this.

Table 1 of the progress report shows effects on cell cycle distribution. For cells treated with only the vehicle DMSO, 20% were in S phase; surprisingly, R1881 at 0.1 nM (the only dose tested) appears to have decreased this to 13%, again raising a question about the effect of DMSO. The S phase fraction was also 12-14% for cells treated with 0.1 or 1 nM TCDD, alone or together with 0.1 nM R1881; this indicates a lack of effect of TCDD and a failure of TCDD to block androgen dependent growth of LNCaP cells, opposite expectations. Paradoxically, for cells treated with10 nM TCDD alone, 20% were in S phase, just like the DMSO control. No statistical analysis was done to determine whether any of these effects were significant. Nonetheless, the PI concluded that in the presence of 0.1 nM R1881 cell cycle arrest was induced in response to 1 and 10 nM TCDD; this conclusion is not supported by the data.

An apoptosis assay, based on annexin V binding and analysis by flow cytometry, was interpreted by the PI to show that very little apoptosis was observed; the PI concludes that cells have been arrested without cell death. The data in Fig. 7 of the progress report, which represent a single experiment, are not adequate to support this conclusion; the annexin-positive fraction ranges from 10% to 27% for different treatments, so it appears that the PI views these values as equivalent to each other.

The next set of experiments tested the effect of benzo[a]pyrene and its 7,8 diol metabolite. The rationale for this approach was not given, and was not part of the original plan. The diol metabolite (at 50 M) was interpreted to decrease LNCaP cell viability only in the presence of R1881 (stated concentration of 0.1 M), but no p values are shown to support this interpretation. The PI also concludes that this combination induced apoptosis (no data shown) and caused S phase arrest (S phase fraction increased from 8% in DMSO to 16% in R1881 + BPdiol). It is not apparent why the PI did not conclude that an increase in the S phase fraction might reflect a stimulatory effect on proliferation.

Summary

The poor quality of data interpretation and experimental design reflect poorly on the mentoring that was to be provided by Dr. Kocarek. It is not likely that useful data have been acquired to support a grant application that would be viewed as competitive.

A first draft manuscript is being prepared. Abstracts were presented in 2003 and 2004 at the AACR meeting.

Rating
This project is rated as unsatisfactory.

Critique 2
The hypothesis proposed by this pilot project was that the Ah receptor inhibits androgen dependent cellular proliferation by regulating RB activity in human prostate carcinoma LNCaP cells. The first specific aim of the project proposed to determine whether the Ah receptor regulated the G1 phase of the cell cycle. Several results are reported in the Progress Report, indicating that TCDD, an Ah receptor agonist, does not significantly affect cell viability of LNCaP cells. Surprisingly, the results reported also show that R1881, a testosterone analog, does not have an effect on these cells, although it has been widely used to induce androgen receptor-dependent proliferation and gene expression in these cells. Dose responses to TCDD in the presence of R1881 indicate that TCDD decreases cell viability and induces the appearance of sub-G1 cells, indicative of apoptosis. Some of the results reported, particularly those describing the cell cycle composition of cells treated with various agents, are particularly surprising. For example, cells treated with DMSO appear to cycle and express high levels of cyclin D1, even though the cells are described as being maintained in charcoal-stripped FBS, which should have removed steroids and blocked them on G0. Notwithstanding, the conclusion is drawn that the cells are arrested, when the evidence clearly demonstrates the opposite. Experiments to study the effect of TCDD on various cell cycle regulators (p16, p21 and p27) lead to inconclusive data, as do experiments to examine the phosphorylation status of RB, which shows high levels of phosphorylation, again indicative of cell cycle progression. During the site visit, the investigator was oblivious to the evidence and insisted that the evidence showed that the cells were arrested. Lack of scientific rigor in data interpretation is the result of a non-existent mentoring relationship.

No progress has taken place in the experiments proposed for the second specific aim due to various problems in the cloning of human RB cDNA in a suitable expression vector.

Rating
Overall progress in this pilot project is deemed unsatisfactory. Data from this work were presented to two AACR meetings and are thought to be at the stage of preparation for publication; however, there are major problems in data interpretation that might preclude publication. Attention should also be given to an extensive body of published evidence on the theme of this project with which the results described in the report seem to be in conflict.

Program note: *Dr. John Reiners (Institute of Environmental Health Sciences), a recognized expert in the role of the Ah receptor in cell cycle regulation, has been consulted on this project with specific regard to interpretation and analysis of data. This refutes the notion that appropriate expertise has not been applied to data interpretation in this project therefore precluding publication of results. [end note]*

Cell Culture Core Facility

Critique 1
The Cell Culture Facility Core at FAMU is well equipped for tissue culture and flow cytometry.

The original grant application described a single Cell Culture and Molecular Methods Core with 2 components, but it has evolved as 2 separate cores, one for cell culture and flow cytometry, the other for molecular methods. The original review had expressed concern about how technology and expertise would be transferred from WSU to FAMU. Although it is not exactly clear how it was done, it does not appear to have been a problem, since the core is up and running and is being utilized. This core facility appears to be a success, and meets the mission of the ARCH program to create research infrastructure at the MSI FAMU.

At the Evaluation visit, an over view of the cell culture facility was presented by Research Associate Dr. Selina Darling-Reed. Dr. Heiman was not present, and it was disclosed that Dr. Heiman will be leaving FAMU for a position elsewhere.

A strategy for continued support of this facility beyond the period of ARCH funding has not been described; this is an effort deserving of institutional support. In addition, a cost-sharing mechanism with investigators who use the facility should be considered. Investigators do their own cell culture manipulations, but Dr. Darling-Reed is the designated operator of the flow cytometer. There should be a mechanism to communicate the availability of this core facility to all potential investigators at FAMU.

Rating
This core facility is rated as satisfactory.

Critique 2
This core facility is deemed as critical for the type of studies that were proposed by the ARCH pilot project investigators. Thus, it is reassuring that the cell culture facility has been established, the equipment is in place, and it is serving multiple ARCH investigators. On the recommendation of the external advisory committee a usage log was initiated and data was included from a six-month log. It appears as though there are seven or eight users. Included in the description of this core facility was documentation of usage of the flow cytometer. Multiple investigators also utilize this facility. During the site visit the facility was visited.

Because of the critical nature of these facilities it is imperative that monies be identified for the maintenance of these core facilities once the ARCH program has ended.

Rating
The Cell Culture Facility is rated as satisfactory.

Molecular Methods Core Facility

Critique 1
In order to overcome lagging progress on the overexpression of CYPs and SULT1E1 in MCF-10A cells, which is necessary for Research Project 1 (Dr. Runge-Morris at WSU) and Pilot Project 1 (Dr. Thomas at FAMU), and the overexpression of the Rb protein in LNCap cells, which is necessary for Pilot Project 2 (Dr. Gragg at FAMU), biotechnologist Dr. Ashok Jain was hired as an Associate in Research in the Molecular Methods Core. After an initial training period under the direction of Dr. Kocarek at WSU, Dr. Jain has made impressive progress in cloning expression constructs for the adenovirus-mediated overexpression of CYP1A1, CYP1A2, CYP2B2, SULT1A1, and Rb. Dr. Jain's progress indicates that the ARCH program at FAMU now has on-campus capabilities in molecular cloning. This development is seen as effective technology transfer from WSU to FAMU.

There is, however, concern about laboratory space allocated for a centralized Molecular Methods Core at FAMU. The space originally provided for the Molecular Methods Core Facility

now houses the Flow Cytometer of the Cell Culture Facility. Electrophoresis and blotting equipment of the Molecular Methods Core Facility has been moved to Dr. Gragg's laboratory, as he is the major user of the equipment; it is assumed that other researchers maintain ready access to it. Dedicated bench space in the 123 Dyson Laboratory (Dr. Reams Laboratory) has been provided for Dr. Jain to carry out molecular biology studies. The lack of a centralized, dedicated laboratory for the Molecular Methods Core where ARCH investigators can utilize the equipment and learn new techniques, and a clearly identified mechanism to expand the equipment available to Core users need to be addressed for the long-term well being of the Core.

Rating
Given the expansion in the use of the techniques of molecular biology at FAMU, the development of the Molecular Methods Core is considered satisfactory.

Critique 2
In the initial application monies were requested to develop a molecular methods facility that would provide the faculty with the basic equipment to perform protein and DNA analysis. With the purchase of a flow cytometer the space that was originally identified for the molecular methods facility was used for the flow cytometer and the electrophoresis equipment was put in Dr. Reams laboratory.

After the first summer, it became apparent that expertise in cloning and gene-transfer was needed at FAMU. Consequently, a faculty member, Dr. Askok Jain, was hired and trained at WSU and this methodology was brought to FAMU. This modification is viewed as a strength. During the site visit Dr. Jain presented data that showed significant progress toward the generation of vectors that are necessary for completion of aim 2 for both Dr. Thomas and Dr. Gragg's pilot projects. Based on the data presented it appears that the technology has been successfully transferred to FAMU.

It is anticipated that an increasing number of investigators will want to take advantage of this resource. Consequently, it is recommended that a designated space be identified for this molecular biology core.

Rating
The molecular biology core is rated as satisfactory.

Institutional Commitment

Success in Attracting Faculty
In both their written document and at the site visit, FAMU described their attempt to recruit faculty that could compete for extramural RO1 funding and that would publish in visible journals. They have been unable to do this thus far for a number of reasons including a hiring freeze by the University. However, they intend to continue their search. They were able to recruit a biotechnologist to handle the cloning tasks that were originally to be performed by WSU.

Release Time
The EAC for the ARCH program recommended to FAMU that release time be increased. The University has instituted a policy that provides release-time to all faculty members with external funding according to the percentage of effort approved in the contract or grant. Faculty members are to be relieved of normal teaching responsibilities in an academic term

commensurate with the amount of release-time generated on a sponsored project(s). Specific arrangements are negotiated when the generated release-time is less than one course load or commences after the start of an academic term. Dr. Reams stated at the site visit that release time was provided for faculty on pilot projects to spend eight weeks at Wayne State in the summers. In addition, Dr. Gragg has been given 10% release time from his teaching duties to work on his ARCH research project.

Status of the Research Infrastructure

Within the past year the University has hired a new Vice President for Research. Upon the recommendation of the ARCH EACFAMU has instituted a new policy that provides faculty members with 15% of recovered indirect costs and provides 10% to departments. A research incentive program has been put in place that will provide productive faculty with a $5,000 cash award. The university administration stated that it provides adequate building infrastructure, well-equipped laboratories and support services to strengthen and expand research development. FAMU has been building research facilities. Many of the investigators in the ARCH program have space in the new facilities. In addition, space was provided for the ARCH Cell Culture Facilities. It is recommended that the Molecular Biology facility, which is currently located in an individual's lab space, be given separate space.

Plans to continue Core Facilities

At this time, there is no charge-back system for the Core facilities and no plans in place to ensure the Cores are self-sustaining. Currently, each of the people who use the Core provides funds for supplies. The PI is aware that formal plans need to be developed that allow the core to have a continuous stream of funds and will work on this over the remaining two years of the grant.

Institutional Support

As part of their commitment to research across the entire campus, in addition the return of 25% of the administrative costs the University has begun to make travel awards and provide lap top computers. The ARCH program has held grant writing workshops and the institution will provide funds to allow PI's to attend grant writing seminars. The administration has also implemented various approaches to mentor junior faculty so that they can become seasoned investigators. These are recently implemented policies that, in part, have been developed in response to suggestions from the ARCH EAC. This is a positive outcome for the ARCH program.

Rating

The institutional commitment made by FAMU on behalf of ARCH is rated as satisfactory.